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Antimicrobial Activity and Spectrum of PPI-0903 (TAK-599), a Novel Cephalosporin, Tested Against a Worldwide Collection of Clinical Strains

HS SADER, LM DESHPANDE, RN JONES

The JONES Group/JMI Laboratories, North Liberty, IA

The JONES Group/JMI Laboratories
North Liberty, IA, USA
www.jmilabs.com
319.665.3370, fax 319.665.3371
ronald-jones@jmilabs.com

ABSTRACT

Background: PPI-0903 is a novel *N*-phosphono type prodrug cephalosporin. PPI-0903M (a bioactive metabolite of PPI-0903) has a high affinity for PBP2' and potent in vitro activity against oxacillin (OXA)-resistant (R) staphylococci.
Methods: A total of 1,478 strains were collected from 80 medical centers (22 countries), mostly in 2003, and tested against >30 antimicrobials by NCCLS reference broth microdilution methods.
Results: PPI-0903M activity against selected organisms is summarized in the Table.

Organism (no.)	PPI-0903M MIC (µg/ml) 50%	90%	Range
S. aureus OXA-susceptible (S; 73)	0.25	0.25	0.03-0.5
S. aureus OXA-R (102)	1	2	0.12-2
VISA or hetero-VISA (100)	1	2	0.25-4
coagulase-negative staphylococci OXA-S (CoNS; 50)	0.06	0.25	≤0.016-0.5
CoNS OXA-R (80)	0.25	0.5	≤0.06-2
S. pneumoniae Penicillin (PEN)-S (SPN; 33)	≤0.016	≤0.016	≤0.016-0.06
SPN PEN-intermediate (50)	0.03	0.06	≤0.016-0.12
SPN PEN-R (50)	0.12	0.25	0.06-0.5
SPN Levofloxacin-non-S (22)	≤0.016	0.12	≤0.016-0.12
SPN Multi-drug-R (MDR) (23)	0.12	0.25	0.12-0.5
viridans gr strept. PEN-S- (VGS; 32)	≤0.016	0.03	≤0.016-1
VGS PEN-R (52)	0.25	1	0.03-8
ß-haemolytic streptococci (78)	≤0.016	≤0.016	≤0.016-0.03
H. influenzae (47)	≤0.016	≤0.016	≤0.016-0.25

Most *Enterobacteriaceae* (221 strains) were very S to PPI-0903M (MIC_{50}, 0.06 – 1 µg/ml), but ESBL-producing strains usually showed elevated PPI-0903M MIC results (MIC_{50}, >32 µg/ml).
Conclusions: PPI-0903M was the most potent cephalosporin tested against staphylococci (MIC_{90}, 0.25 - 2 µg/ml), especially OXA-R strains and contemporary MDR strains; and reduced S to vancomycin or quinupristin/dalfopristin did not affect PPI-0903M activity. Further evaluations should be performed to establish the clinical role of this promising cephalosporin.

INTRODUCTION

PPI-0903 (formerly TAK-599) is a novel *N*-phosphono type prodrug cephalosporin. Its active form PPI-0903M (formerly T-91825) is released in vivo upon hydrolysis of the phosphonate group (Figure 1). Preliminary in vitro studies have indicated that this compound has a high affinity for PBP2' or PBP2A and shows a potent in vitro activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and many other Gram-positive organisms.

We evaluated the in vitro activity of PPI-0903M and numerous comparator agents against selected contemporary clinical isolates, including various resistant gram-positive cocci. A total of 1,478 strains were tested by reference methods with in vitro results interpreted by current published criteria. The objective of this study is to profile PPI-0903 against common pathogens, especially drug resistant gram-positive cocci in comparison with other anti-gram positive antibiotics and cephalosporins.

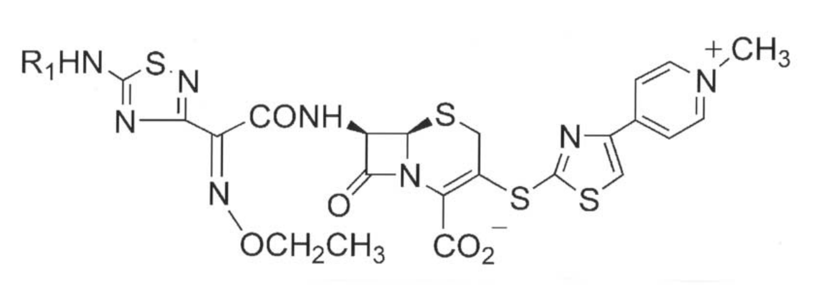
MATERIALS AND METHODS

Antimicrobials tested. The PPI-0903M reagent grade compound was provided by Peninsula Pharmaceutical Inc. (Alameda, CA) and manufactured by Takeda Pharmaceutical Inc (Osaka, Japan). Comparator agents were purchased from Sigma Chemical Co. (St. Louis, MO, USA) or obtained from their respective manufacturers in the USA. A total of 31 comparators were evaluated depending upon the species tested.

Organisms tested. The collection of 1478 strains was selected from various surveillance networks and other specialized collections to include organisms isolated from human infections. Only non-duplicate isolates judged to be clinically significant by local criteria were included in the study. The vast majority of isolates were collected in the last 12-24 months (since January 2002). Clinical isolates with specific antimicrobial resistance patterns were selected for the study, including staphylococci with decreased susceptibility to vancomycin or quinupristin/dalfopristin, streptococci with decreased susceptibility to levofloxacin or quinupristin/dalfopristin, multi-drug resistant (MDR) *Streptococcus pneumoniae*, vancomycin-resistant enterococci, extended-spectrum ß-lactamase (ESBL) and/or ampC producing *Enterobacteriaceae*, and ampicillin-resistant *Haemophilus influenzae*.

Susceptibility testing methods. PPI-0903M minimum inhibitory concentrations (MICs) were determined by the reference methods according to procedures recommended by the National Committee for Clinical Laboratory Standards (NCCLS). Supplemented 5% lysed horse blood was added for testing *Streptococcus* spp. and *Corynebacterium* spp., and Haemophilus Test Medium (HTM) was utilized for testing *H. influenzae*. The MIC values were interpreted according to NCCLS criteria [2004]. Quality control (QC) was monitored using the following organisms: *S. pneumoniae* ATCC 49619, *Enterococcus faecalis* ATCC 29212, *S. aureus* ATCC 29213, *Escherichia coli* ATCC 25923, and *Pseudomonas aeruginosa* ATCC 27853.

Figure 1. Chemical structure of PPI-0903 (formerly TAK-599) and PPI-0903M (T-91825).



1 (TAK-599); R_1=PO(OH)$_2$ (Acetic acid solvate)
2a (T-91825); R_1=H

Table 1. In vitro activity of PPI-0903M and comparator antimicrobial agents tested against selected Gram-positive species.

Organism (no. tested)	Antimicrobial agent	MIC (µg/ml) 50%	90%	Range	% by category Susceptible	Resistant
Methicillin-susceptible *S. aureus* (73)	PPI-0903M	0.25	0.25	0.03-0.5	-[a]	-
	Cefepime	2	4	0.25-16	98.6	0.0
	Ceftriaxone	4	4	0.5-16	98.6	0.0
	Ceftazidime	8	16	2-16	89.0	0.0
Methicillin-resistant *S. aureus* (102)	PPI-0903M	1	2	0.12-2	-	-
	Cefepime	>16	>16	1->16	(26.5)[b]	(60.8)[b]
	Ceftriaxone	>32	>32	4->32	(11.8)[b]	(60.8)[b]
	Ceftazidime	>16	>16	8->16	(2.0)[b]	(86.3)[b]
hetero-VISA/VISA[c] (100)	PPI-0903M	1	2	0.25-4	-	-
	Cefepime	>16	>16	4->16	7.0	91.0
	Ceftriaxone	>32	>32	4->32	4.0	93.0
	Ceftazidime	>16	>16	16->16	0.0	97.0
	Oxacillin	>2	>2	≤0.25->2	12.0	88.0
	Vancomycin	2	2	0.5-8	98.0	0.0
Q/D-non-susceptible *S. aureus* (11)[d]	PPI-0903M	1	1	0.25-1	-	-
	Cefepime	>16	>16	2->16	(18.2)[b]	63.6[b]
	Ceftriaxone	>32	>32	8->32	(9.1)[b]	72.7[b]
	Ceftazidime	>16	>16	8->16	(9.1)[b]	90.9[b]
	Quinupristin/Dalfopristin	8	>8	2->8	0.0	72.7
Methicillin-susceptible CoNS (50)	PPI-0903M	0.06	0.25	≤0.016-0.5	-	-
	Cefepime	1	2	0.25-2	100.0	0.0
	Ceftriaxone	2	4	0.5-8	100.0	0.0
	Ceftazidime	4	8	≤1-16	98.2	0.0
Methicillin-resistant CoNS (80)	PPI-0903M	0.25	0.5	≤0.016-2	-	-
	Cefepime	4	8	1->16	(92.5)[b]	(6.3)[b]
	Ceftriaxone	8	32	4->32	(55.0)[b]	(5.0)[b]
	Ceftazidime	16	>16	8->16	(16.3)[b]	(25.0)[b]
CoNS heteroresistance vancomycin (51)[e]	PPI-0903M	1	2	≤0.016-2	-	-
	Cefepime	>16	>16	0.5->16	31.4	62.7
	Ceftriaxone	>32	>32	1->32	15.7	66.7
	Ceftazidime	>16	>16	8->16	9.8	80.4
	Oxacillin	>8	>8	≤0.25->8	9.8	90.2
	Vancomycin	4	4	4	100.0	0.0
Q/D-non-susceptible CoNS (15)	PPI-0903M	0.5	1	0.12-2	-	-
	Cefepime	8	>16	1->16	(60.0)[b]	(26.7)[b]
	Ceftriaxone	32	>32	8->32	(33.3)[b]	(40.0)[b]
	Ceftazidime	>16	>16	16->16	(0.0)[b]	(54.5)[b]
	Oxacillin	>8	>8	0.5->8	0.0	100.0
	Quinupristin/Dalfopristin	4	>8	2->8	0.0	80.0
Penicillin-susceptible *S. pneumoniae* (33)	PPI-0903M	≤0.016	≤0.016	≤0.016-0.06	-	-
	Cefepime[f]	≤0.06	0.25	≤0.06-0.5	100.0	0.0
	Ceftriaxone[f]	0.016	0.06	0.016-0.5	100.0	0.0
Penicillin-intermediate *S. pneumoniae* (50)	PPI-0903M	0.03	0.06	≤0.016-0.12	-	-
	Cefepime[f]	0.25	1	≤0.06-4	95.9	2.0
	Ceftriaxone[f]	0.25	0.5	0.03-1	100.0	0.0
Penicillin-resistant *S. pneumoniae* (50)	PPI-0903M	0.12	0.25	0.06-0.5	-	-
	Cefepime[f]	1	2	0.25-4	78.0	2.0
	Ceftriaxone[f]	1	2	≤0.008-8	82.0	8.0
Levofloxacin-non-susceptible *S. pneumoniae* (22)	PPI-0903M	≤0.016	0.12	≤0.016-0.12	-	-
	Cefepime[f]	≤0.06	0.5	≤0.06-1	100.0	0.0
	Ceftriaxone[f]	0.03	0.5	≤0.008-1	100.0	0.0
	Levofloxacin	>4	>4	4->4	0.0	86.4
MDR *S. pneumoniae* (23)[g]	PPI-0903M	0.12	0.25	0.12-0.5	-	-
	Cefepime[f]	1	2	0.5-4	73.9	4.3
	Ceftriaxone[f]	1	4	≤0.008-8	73.9	13.0
	Levofloxacin	1	1	0.5-4	95.7	0.0
	Penicillin	4	4	2-4	0.0	100.0
	Erythromycin	>32	>32	32->32	0.0	100.0
	Clindamycin	>2	>2	2->2	0.0	100.0
	Tetracycline	>16	>16	8->16	0.0	100.0
	Trim/Sulfa	>4	>4	4->4	0.0	100.0
Penicillin-susceptible viridans group streptococci (32)	PPI-0903M	≤0.016	0.03	≤0.016-1	-	-
	Cefepime	≤0.12	0.25	≤0.12-0.5	100.0	0.0
	Ceftriaxone	≤0.25	≤0.25	≤0.25-0.5	100.0	0.0
	Ceftazidime	≤1	2	≤1->16	-	-
Penicillin-intermediate viridans group streptococci (53)	PPI-0903M	0.03	0.12	≤0.016-0.5	-	-
	Cefepime	0.5	1	≤0.12-4	90.6	1.9
	Ceftriaxone	0.5	2	≤0.25-4	90.6	1.9
	Ceftazidime	4	8	≤1->16	-	-
Penicillin-resistant viridans group streptococci (52)	PPI-0903M	0.25	1	0.03-8	-	-
	Cefepime	4	8	1->16	21.2	53.8
	Ceftriaxone	4	16	1->32	9.8	58.8
	Ceftazidime	>16	>16	≤2->16	-	-
Levofloxacin-non-susceptible, viridans group streptococci (20)	PPI-0903M	0.06	0.25	≤0.016-1	-	-
	Cefepime	0.25	4	≤0.12-8	75.0	15.0
	Ceftriaxone	≤0.25	2	≤0.25-16	75.0	6.2
	Ceftazidime	2	>16	≤2->16	-	-
	Penicillin	0.06	4	≤0.03-16	55.0	15.0
	Levofloxacin	>4	>4	4->4	0.0	75.0
ß-haemolytic streptococci (78)[h]	PPI-0903M	≤0.016	≤0.016	≤0.016-0.03	-	-
	Cefepime	≤0.12	0.5	≤0.12-0.5	100.0	0.0
	Ceftriaxone	≤0.25	≤0.25	≤0.25	100.0	0.0
	Ceftazidime	≤1	4	≤1-16	-	-
	Penicillin	≤0.016	0.12	≤0.016-0.12	100.0	0.0
Levofloxacin-resistant ß-haemolytic streptococci. (10)[i]	PPI-0903M	≤0.016	≤0.016	≤0.016-0.03	-	-
	Cefepime	≤0.12	0.25	≤0.12-0.25	100.0	0.0
	Ceftriaxone	≤0.25	≤0.25	≤0.25	100.0	0.0
	Ceftazidime	≤2	≤2	≤2	-	-
	Penicillin	0.03	0.06	≤0.016-0.12	100.0	0.0
	Levofloxacin	>4	>4	>4	0.0	100.0
Q/D-non-susceptible streptococci (6)[j]	PPI-0903M	≤0.016	-	≤0.016-8	-	-
	Cefepime	0.12	-	≤0.12->16	50.0	50.0
	Ceftriaxone	32	-	≤0.25->32	40.0	60.0
	Ceftazidime	>16	-	≤2->16	-	-
	Penicillin	0.12	-	≤0.016->32	50.0	50.0
	Quinupristin/Dalfopristin	4	-	2-4	0.0	66.7

a. - = No breakpoints have been established by the NCCLS [2004].
b. Oxacillin-resistant *S. aureus* should be considered resistant to all ß-lactams according to NCCLS [2004] recommendations.
c. Includes 19 well-characterized vancomycin-intermediate *S. aureus* (VISA) strains and 81 hetero (h)-VISA strains using the PAP method (Wooton et al., J. Antimicrob. Chemother. 47:399-403, 2001) and results reported in an evaluation of AZD2563, an oxazolidinone (Howe et al., Antimicrob. Agents Chemother. 47:3651-3652, 2003).
d. Quinupristin/dalfopristin MIC ≥2 µg/ml.
e. Vancomycin MIC at 4 µg/ml.
f. Breakpoints for non-meningitis isolates were applied [NCCLS, 2004].
g. Resistant to penicillin, erythromycin, clarithromycin, clindamycin, tetracycline and trimethoprim/sulfamethoxazole.
h. Includes 22 isolates of group A, 26 isolates of group B, and 20 isolates of other ß-haemolytic streptococci.
i. Includes one group A, five group B, one group C, two group G, and one ß-haemolytic strain which group has not been identified.
j. Quinupristin/dalfopristin MIC ≥2 µg/ml. Includes four *S. mitis* and two *S. bovis*.

Table 2. In vitro activity of PPI-0903M and comparators tested against Gram-negative pathogens related to respiratory tract infections and meningitis.

Organism (no. tested)	Antimicrobial agent	MIC (µg/ml) 50%	90%	Range	% by category Susceptible	Resistant
Non-ß-lactamase producing *H. influenzae* (23)	PPI-0903M	≤0.016	≤0.016	≤0.016	-[a]	-
	Cefepime	≤0.06	0.12	≤0.06-0.12	100.0	0.0
	Ceftriaxone	≤0.008	≤0.008	≤0.008-0.016	100.0	0.0
	Ampicillin	≤0.5	1	≤0.5-1	100.0	0.0
ß-lactamase-producing *H. influenzae* (24)	PPI-0903M	≤0.016	≤0.016	≤0.016-0.25	-	-
	Cefepime	≤0.06	0.12	≤0.06-1	100.0	0.0
	Ceftriaxone	≤0.008	0.016	≤0.008-0.06	100.0	0.0
	Ampicillin	>4	>4	2->4	0.0	97.1
BLNAR *H. influenzae* (30)[b]	PPI-0903M	≤0.016	0.03	≤0.016-0.03	-	-
	Cefepime	0.25	0.5	≤0.06-1	100.0	0.0
	Ceftriaxone	0.016	0.6	≤0.008-2	100.0	0.0
	Ampicillin	2	4	2->4	0.0	23.3
M. catarrhalis (25)[c]	PPI-0903M	0.06	0.12	≤0.016-0.12	-	-
	Cefepime	0.25	1	≤0.06-2	100.0	0.0
	Ceftriaxone	0.06	0.5	≤0.008-1	100.0	0.0
	Ampicillin	≤0.5	2	≤0.5->4	4.0	96.0
Neisseria meningitidis (10)	PPI-0903M	≤0.016	≤0.016	≤0.016	-	-
	Cefepime	≤0.12	≤0.12	≤0.12	-	-
	Ceftriaxone	≤0.25	≤0.25	≤0.25	-	-
	Ceftazidime	≤1	≤1	≤1	-	-
	Penicillin	≤0.016	0.25	≤0.016-0.25	-	-

a. - = No breakpoints have been established by the NCCLS [2004].
b. ß-lactamase-negative ampicillin-resistant strains.
c. *Haemophilus influenzae* breakpoints were applied [NCCLS, 2004] and the ß-lactamase test for ampicillin.

Table 3. In vitro activity of PPI-0903M and comparators tested against selected *Enterobacteriaceae* species.

Organism (no. tested)	Antimicrobial agent	MIC (µg/ml) 50%	90%	Range	% by category Susceptible	Resistant
Citrobacter freundii (20)	PPI-0903M	0.12	2	0.06->32	-[a]	-
	Cefepime	≤0.12	0.25	≤0.12-1	100.0	0.0
	Ceftriaxone	≤0.25	0.5	≤0.25-1	100.0	0.0
	Ceftazidime	≤1	2	≤1-4	100.0	0.0
Enterobacter cloacae (23)[b]	PPI-0903M	0.12	32	0.03->32	-	-
	Cefepime	≤0.12	2	≤0.12-4	100.0	0.0
	Ceftriaxone	≤0.25	16	≤0.25->32	87.0[a]	8.7
	Ceftazidime	≤1	>16	≤1->16	87.0[a]	13.0
ESBL-producing *E. cloacae* (15)	PPI-0903M	>32	>32	4->32	-	-
	Cefepime	16	>16	8->16	40.0	33.3
	Ceftriaxone	>32	>32	16->32	0.0	86.7
	Ceftazidime	>16	>16	2->16	33.3	53.3
E. coli (WT, 20)[c]	PPI-0903M	0.06	0.12	≤0.016-0.25	-	-
	Cefepime	≤0.12	≤0.12	≤0.12	100.0	0.0
	Ceftriaxone	≤0.25	≤0.25	≤0.25	100.0	0.0
	Ceftazidime	≤1	≤1	≤1	100.0	0.0
ESBL-producing *E. coli* (15)	PPI-0903M	>32	>32	0.5->32	-	-
	Cefepime	16	>16	≤0.12->16	46.7	40.0
	Ceftriaxone	>32	>32	≤0.25->32	40.0	60.0
	Ceftazidime	8	>16	≤1->16	53.3	20.0
Klebsiella pneumoniae (WT, 21)[c]	PPI-0903M	0.06	0.5	0.03-4	-	-
	Cefepime	≤0.12	≤0.12	≤0.12-0.25	100.0	0.0
	Ceftriaxone	≤0.25	≤0.25	≤0.25	100.0	0.0
	Ceftazidime	≤1	≤1	≤1	100.0	0.0
ESBL-producing *K. pneumoniae* (15)	PPI-0903M	>32	>32	32->32	-	-
	Cefepime	8	>16	2->16	60.0	20.0
	Ceftriaxone	>32	>32	16->32	0.0	66.7
	Ceftazidime	>16	>16	≤1->16	40.0	53.3
Morganella morganii (WT, 20)[c]	PPI-0903M	0.06	0.12	0.03-0.5	-	-
	Cefepime	≤0.12	≤0.12	≤0.12	100.0	0.0
	Ceftriaxone	≤0.25	≤0.25	≤0.25-0.5	100.0	0.0
	Ceftazidime	≤1	≤1	≤1	100.0	0.0
Proteus mirabilis (WT, 20)[c]	PPI-0903M	0.12	0.12	0.03-4	-	-
	Cefepime	≤0.12	≤0.12	≤0.12	100.0	0.0
	Ceftriaxone	≤0.25	≤0.25	≤0.25-0.5	100.0	0.0
	Ceftazidime	≤1	≤1	≤1	100.0	0.0
ESBL-producing *P. mirabilis* (10)	PPI-0903M	>32	>32	4->32	-	-
	Cefepime	>16	>16	>16	0.0	100.0
	Ceftriaxone	>32	>32	1->32	30.0	70.0
	Ceftazidime	4	16	≤1->16	80.0	10.0
Providencia spp./*P. vulgaris* (22)[d]	PPI-0903M	1	>32[a]	0.03->32	-	-
	Cefepime	≤0.12	1	≤0.12-8	100.0	0.0
	Ceftriaxone	≤0.25	4	≤0.25-32	90.9	9.1
	Ceftazidime	≤1	≤1	≤1-8	100.0	0.0
Serratia marcescens (WT, 20)[c]	PPI-0903M	0.5	2	0.12-8	-	-
	Cefepime	≤0.12	0.25	≤0.12-0.5	100.0	0.0
	Ceftriaxone	≤0.25	1	≤0.25-8	100.0	0.0
	Ceftazidime	≤1	≤1	≤1	100.0	0.0

a. - = No breakpoints have been established by the NCCLS [2004].
b. 13% of isolates produced a stably derepressed AmpC enzyme.
c. WT, wild type.
d. Two *Proteus vulgaris* and two *Providencia stuartii* isolates had PPI-0903M MICs of > 32 µg/ml.

RESULTS

- PPI-0903M was the most potent cephalosporin tested against staphylococci, especially methicillin-resistant strains. PPI-0903M was eight- to >16-fold more potent than cefepime, and 16- to >32-fold more potent than ceftriaxone against these pathogens (Table 1).
- Penicillin-susceptible *S. pneumoniae* strains were very susceptible to all three cephalosporins tested (PPI-0903M, cefepime and ceftriaxone), and PPI-0903M was the most potent cephalosporin against penicillin-intermediate (MIC_{90}, 0.06 µg/ml), penicillin-resistant (MIC_{90}, 0.25 µg/ml) and multi-drug resistant (MIC_{90}, 0.25 µg/ml) strains.
- PPI-0903M was eight-fold more potent than cefepime or ceftriaxone against penicillin-intermediate, penicillin-resistant and levofloxacin-non-susceptible viridans group streptococci.
- ß-haemolytic streptococci (groups A, B, C, F, and G) were markedly susceptible to PPI-0903M (MIC_{90}, ≤0.016 µg/ml) and all other cephalosporins evaluated. In addition, PPI-0903M was more potent than either cefepime or ceftriaxone against a small group of quinupristin/dalfopristin non-susceptible strains.
- PPI-0903M was more active than both cefepime and ceftazidime against vancomycin-susceptible and –resistant *E. faecalis*. Many *E. faecalis* isolates showed relatively low PPI-0903M MIC (MIC_{50}, 2- 4 µg/ml). However, like other ß-lactams, the vast majority of *E. faecium* isolates (24 strains tested) showed high MIC values for PPI-0903M (MIC_{90}, >32 µg/ml). Linezolid-resistant enterococci (10 strains) also showed high MIC results for PPI-0903M (MIC_{50}, 16 µg/ml and MIC_{90}, >32 µg/ml; data not shown).
- PPI-0903M, cefepime and ceftriaxone were highly active against *H. influenzae*, *Moraxella catarrhalis* and *Neisseria meningitidis*. Against BLNAR strains of *H. influenzae*, PPI-0903M was the most potent compound tested with a MIC_{90} of 0.03 µg/ml (Table 2).
- The vast majority of *C. freundii* (MIC_{90}, 2 µg/ml), non-ESBL-producing *E. coli* (MIC_{90}, 0.12 µg/ml) and *K. pneumoniae* (MIC_{90}, 0.5 µg/ml); *Morganella morganii* (MIC_{90}, 0.12 µg/ml), *Proteus mirabilis* (MIC_{90}, 0.12 µg/ml) and *Serratia marcescens* (MIC_{90}, 2 µg/ml) were inhibited at 2 µg/ml of PPI-0903M. However, PPI-0903M MIC results were higher for *E. cloacae* (MIC_{90}, 32 µg/ml), *Proteus vulgaris* / *Providencia* spp. (MIC_{90}, >32 µg/ml), and ESBL-producing strains regardless of species (Table 3). These results were similar to those of third-generation cephalosporins.
- Non-fermentative Gram-negative bacilli (60 strains) showed relatively low susceptibility to PPI-0903M (MIC_{50}, 16->32 µg/ml and MIC_{90}, >32 µg/ml) as well as to the third-generation cephalosporin ceftriaxone (data not shown).
- PPI-0903M showed excellent activity against anaerobic Gram-positive isolates (MIC_{50}, 0.06 µg/ml), but *B. fragilis* and *Prevotella* spp. showed generally higher PPI-0903M MIC results (data not shown).

CONCLUSIONS

- *Staphylococcus* spp., including MRSA and coagulase-negative staphylococci, appeared to be particularly susceptible to PPI-0903M as compared to other cephalosporins tested. This finding is important in light of the increasing occurrence of MRSA in community and nosocomial infections.
- PPI-0903M also showed potent activity against MDR streptococci, enterococci that are susceptible to penicillins and some rarer Gram-positive species.
- Gram-negative pathogens associated with community-acquired respiratory tract infections were also PPI-0903M-susceptible.
- Based upon the in vitro data, PPI-0903M appears to offer advantages in potency and spectrum when compared to currently marketed cephalosporins, against a specific subgroup of Gram-positive organisms that includes methicillin-resistant staphylococci where resistance to vancomycin, once considered the drug of last resort, has been documented in recent years. Further evaluations should be performed to establish the clinical role of this promising cephalosporin.

REFERENCES

Iizawa Y, Nagai J, Ishikawa T, Hashiguchi S, Miyake A, Nakao M, Okonogi K. (2002). TAK-599, a novel N-phosphone type prodrug of anti-MRSA cephalosporin T-91825: In vitro and in vivo antibacterial activity. In: *42nd Interscience Conference on Antimicrobial Agents and Chemotherapy*, San Diego, CA, Sept. 27-30.

Ishikawa T, Matsunaga N, Tawada H, Kuroda N, Nakayama Y, Ishibashi Y, Tomimoto M, Ikeda Y, Tagawa Y, Iizawa Y, Okonogi K, Hashiguchi S, Miyake A. (2003). TAK-599, a novel N-phosphono type prodrug of anti-MRSA cephalosporin T-91825: Synthesis, physicochemical and pharmacological properties. *Bioorganic and Medicinal Chemistry* 11:2427-2437.

National Committee for Clinical Laboratory Standards. (2003). *Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard - sixth edition. Approved document M7-A6*. Wayne, PA:NCCLS.

National Committee for Clinical Laboratory Standards. (2004). *Performance standards for antimicrobial susceptibility testing, 13th informational supplement M100-S14*. Wayne, PA:NCCLS.

National Committee for Clinical Laboratory Standards. (2004). *Methods for antimicrobial susceptibility testing of anaerobic bacteria. Approved standard, 6th edition M11-A6*. Wayne, PA:NCCLS.